UNC studies link viral infection response to smoking and nutrition

By Richard Sloane

In addition to the long-term harmful effects of smoking, recent findings suggest that exposure to tobacco smoke may also affect how otherwise healthy people respond to flu infection.

According to NIEHS grantee Ilona Jaspers, Ph.D., who spoke March 8 at Duke University on "Inhaled pollutants and host defense: studies from right under your nose," the effects are the result of oxidant-driven gene expression changes that directly inhibit antiviral pathways in human respiratory epithelium infected with influenza virus.

Jaspers *(http://www.med.unc.edu/microimm/faculty/immunology/ilona-jaspers-ph.d)* and her team at the University of North Carolina (UNC) at Chapel Hill Center for Environmental Medicine, Asthma, and Lung Biology aren't just looking at the negative impact of tobacco smoke exposure. They're also conducting research on an antioxidant micronutrient found in cruciferous vegetables, such as broccoli and cauliflower (see text box), that may improve host response and lessen the severity of effects from flu infection, which makes thousands of Americans ill each year and can even result in death for people with compromised immune systems.

Using exposure chambers available in the U.S. Environmental Protection Agency Human Studies Facility at UNC, Jaspers also studies how ambient air pollutants, such as ozone and diesel exhaust, modify innate host defense responses in the context of viral infections. (Photo courtesy of Steve McCaw)

Flu's portal of entry — the nose

Jaspers' studies focused on nasal epithelial cells, since they are the primary targets of respiratory viruses. She explained that in order to study the defense responses, her team used two experimental models. The *in vitro* model uses differentiated human airway epithelial cells, while the *in vivo* model involved an inoculation technique, in human volunteers, with the live attenuated influenza virus (LAIV) vaccine.

LAIV is designed to replicate best in the nasal cavity, which is easy to sample reliably and repeatedly, Jaspers explained. It's also the predominant target for LAIV and offers a very safe way to study influenza infection *in vivo*. The team collected samples by nasal lavage with a saline solution, a simple non-invasive procedure for nasal flushing similar to using a neti pot, from three groups of subjects — smokers, non-smokers, and people who don't smoke but are exposed to second-hand smoke at home or at work.

Jaspers' presentation was part of the Duke University Integrated Toxicology and Environmental Health Program Seminar Series. (Photo courtesy of Steve McCaw)

The samples were analyzed using flow cytometry and various molecular techniques, to determine markers of inflammation. The team found differences in indicators of inflammation. "Nasal epithelial cell populations somehow seemed to lose their ability to effectively communicate with their neighboring cells in smoke-exposed subjects," Jaspers said.

LAIV replication was higher in both smokers and those exposed to second-hand smoke than in non-smokers, indicating that the body's natural immunity to the virus was suppressed in both passive and active smokers. Smokers also displayed response suppression in dendritic, natural killer, and T cells, which are all critically important players in human immune response.

Gene expression changes

According to Jaspers, nasal viral exposure normally induces the production of an antiviral mediator in the nasal epithelium called interferon, an important component of the body's immune system that limits the ability of a virus to self-replicate. In the nasal epithelium of smokers, mechanisms mediating the production of interferon appear to be blunted.

This effect appears to be, at least partially, linked to changes in the methylation of genes, an epigenetic effect of exposure to smoke. Methylation of genes takes place when a methyl group links to a DNA molecule, which can result in silencing of that gene. Jaspers said that, based on previous studies conducted at Boston University, with smoking cessation, total gene recovery or reversibility of damage from smoke exposure is possible for some genes. For others, it may be semireversible and, in some cases, not reversible at all.

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Exploring secondary prevention

Tobacco smoke is a strong oxidant, and the optimal way to protect people from its effects is to avoid exposure in the first place. But individuals won't or can't always quit smoking or avoid exposure to second-hand smoke.

What Jaspers is now interested in exploring is whether nutritional antioxidants can diminish the harmful effects of tobacco smoke on the nasal epithelium and improve host response to influenza infection. To find out, she is experimenting with a micronutrient called sulforaphane that is found in cruciferous vegetables. All cruciferous vegetables contain sulforaphane, but it is particularly abundant in broccoli.

As Jaspers explained, laboratory studies and NIEHS-funded clinical studies in China have shown that higher intake of sulforaphane may aid in detoxification of cancer-causing contaminants. So Jaspers' team prepared what they call brocco shakes, broccoli sprouts blended with water, for volunteers to consume three days in a row. Controls drank a placebo drink containing shakes made from other sprouts.

At the end of the three days, Jaspers' team collected and analyzed nasal lavage samples from the volunteers. Those who consumed the brocco shakes demonstrated higher antioxidant gene expression patterns than the control group. Jaspers said the results are promising and more studies are forthcoming.

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